FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

For submissions to CBER and CDER

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May 21st, 2021

AGENDA

- TRC Background and What's New
- Overview of the Technical Rejection Criteria (TRC) & Effective Date
- TRC Warning Metrics
- CDER SEND Requirements and TRC
- Preparing a Study Using the Self-Check Worksheet
- Creating a Simplified TS.XPT File
- Frequently Asked Questions

TRC BACKGROUND AND WHAT'S NEW

FDA GUIDANCE AND DATA STANDARDS CATALOG

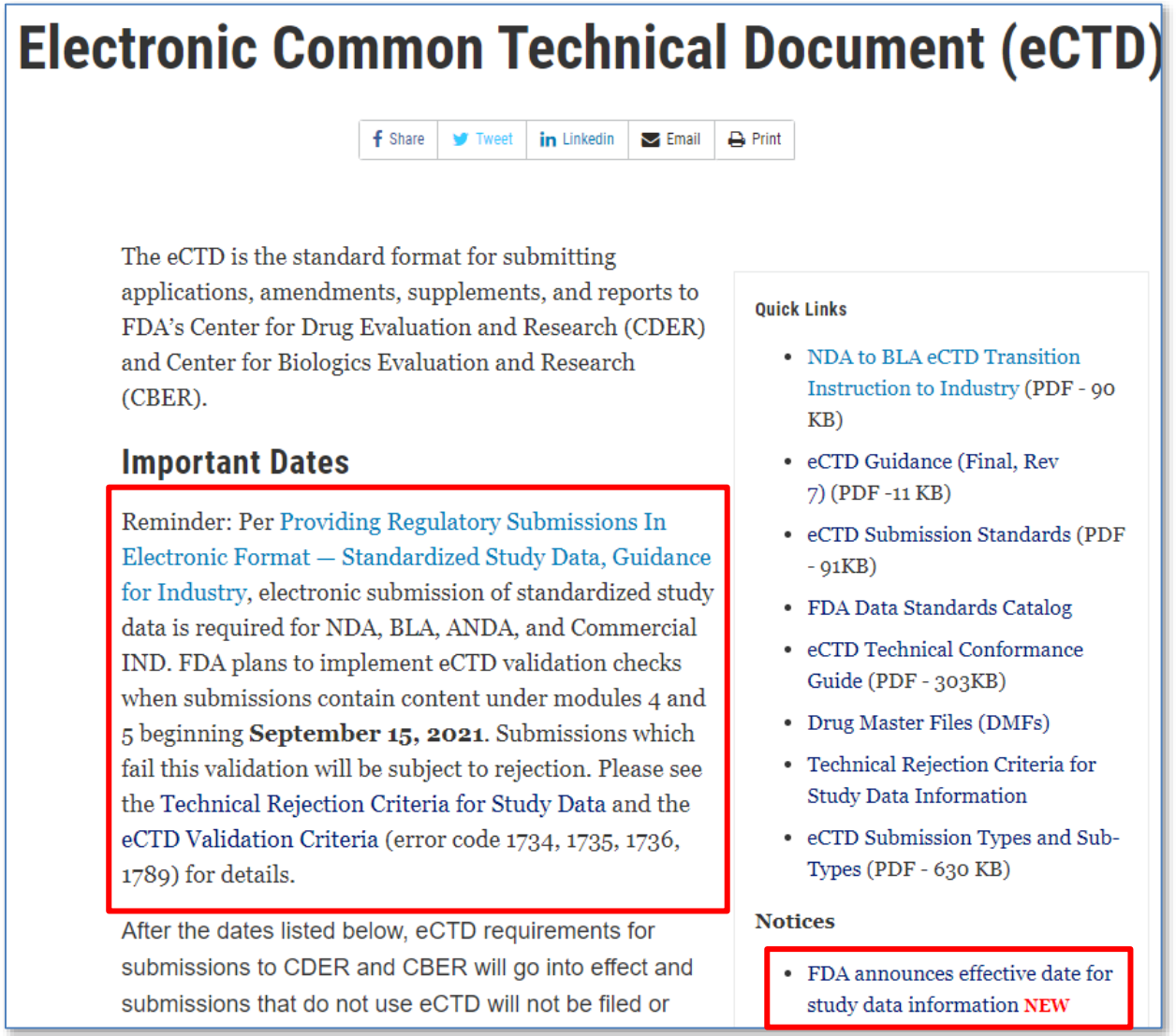
- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type
- FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry” in December 2014 (updated in October 2020)
- Sponsors must conform to standards in the FDA Data Standards Catalog:
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017
- **Technical Rejection Criteria for Study Data developed to help industry understand how FDA is using eCTD validations to check conformance**

WHAT'S NEW

- FDA Data Standards Catalog was updated (March 2021)
  - Contains footnote re: Simplified TS.XPT file
- TRC effective date published: Electronic Common Technical Document (eCTD) web page, Specification for eCTD Validation Criteria, and within the TRC document
- Warning notice will be sent between March 15th and Sept. 15th, 2021 for submissions failing eCTD validations in TRC
- **Starting Sept 15th, 2021**, if a submission fails eCTD validations in TRC, CDER and CBER will reject

ELECTRONIC COMMON TECHNICAL DOCUMENT (ECTD) WEB PAGE

The effective date for the Technical Rejection Criteria was published to FDA's Electronic Common Technical Document (eCTD) web page.



Electronic Common Technical Document (eCTD)

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The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Important Dates

Reminder: Per Providing Regulatory Submissions In Electronic Format — Standardized Study Data, Guidance for Industry, electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the Technical Rejection Criteria for Study Data and the eCTD Validation Criteria (error code 1734, 1735, 1736, 1789) for details.

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or

Quick Links

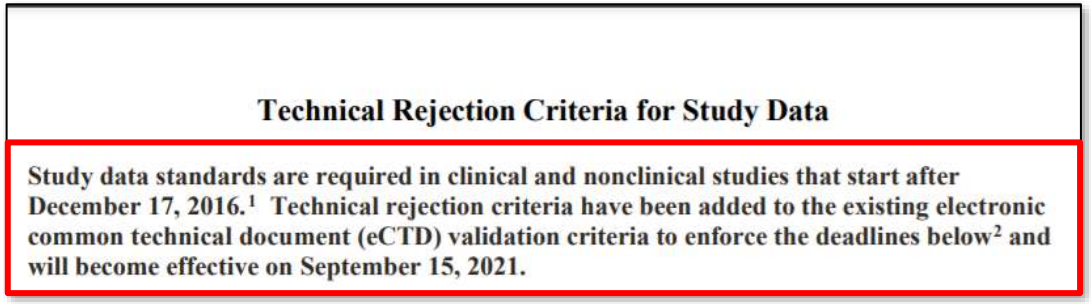
- NDA to BLA eCTD Transition Instruction to Industry (PDF - 90 KB)
- eCTD Guidance (Final, Rev 7) (PDF -11 KB)
- eCTD Submission Standards (PDF - 91KB)
- FDA Data Standards Catalog
- eCTD Technical Conformance Guide (PDF - 303KB)
- Drug Master Files (DMFs)
- Technical Rejection Criteria for Study Data Information
- eCTD Submission Types and Sub-Types (PDF - 630 KB)

Notices

- FDA announces effective date for study data information NEW

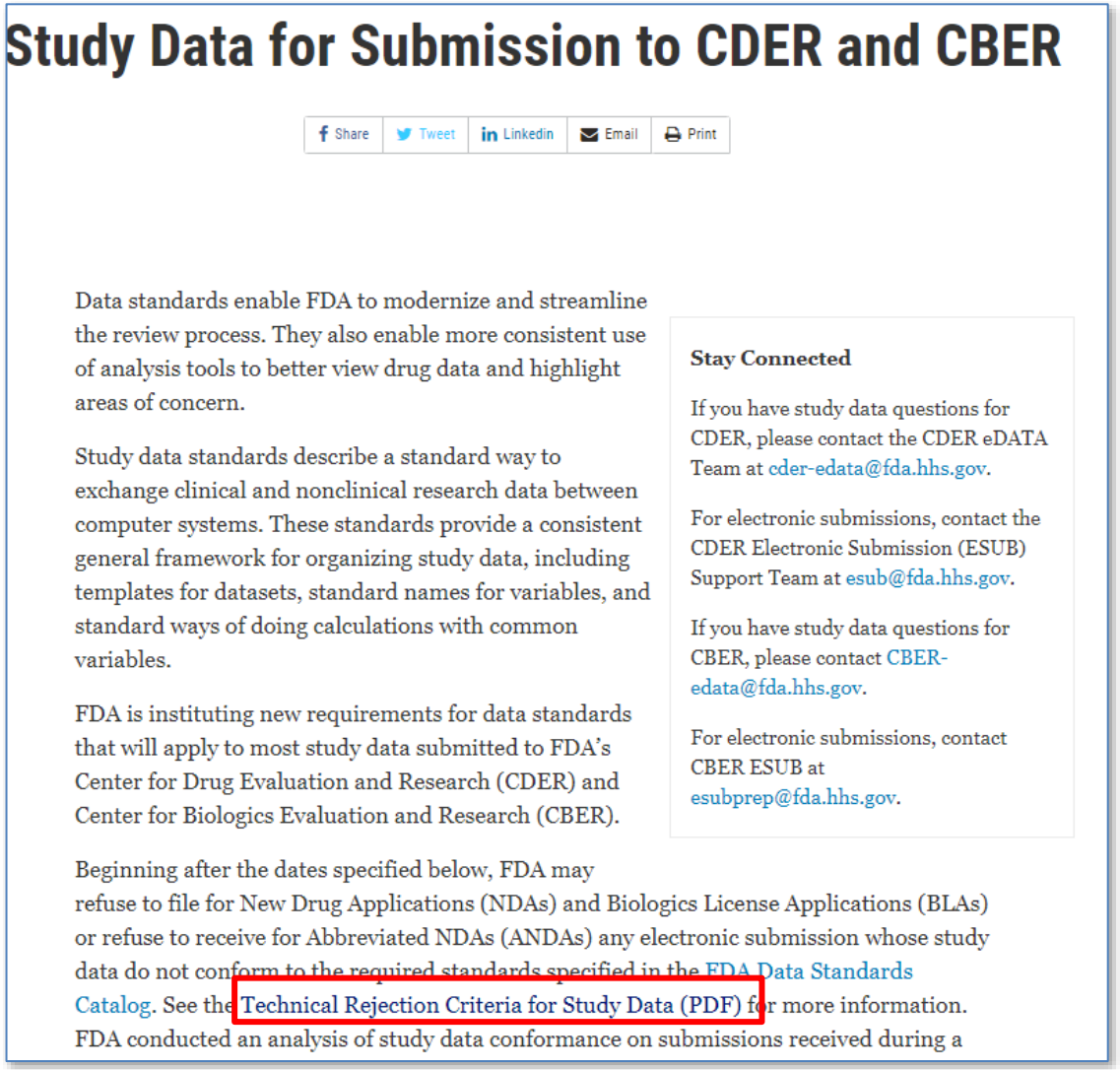
TECHNICAL REJECTION CRITERIA UPDATED

The Technical Rejection Criteria and Specification for eCTD Validation Criteria were updated to reflect the effective dates for implementation of the eCTD validations and published to FDA's website on the *Study Data for Submission to CDER and CBER* web page.



Technical Rejection Criteria for Study Data

Study data standards are required in clinical and nonclinical studies that start after December 17, 2016.[1] Technical rejection criteria have been added to the existing electronic common technical document (eCTD) validation criteria to enforce the deadlines below[2] and will become effective on September 15, 2021.



Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the Technical Rejection Criteria for Study Data (PDF) for more information. FDA conducted an analysis of study data conformance on submissions received during a

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

OVERVIEW OF THE TECHNICAL REJECTION CRITERIA (TRC) & EFFECTIVE DATE

TRC IMPORTANT DATES

Data Standard Requirements	TRC Implementation
12/17/2016 – Studies that start on/after require standardized data for NDAs, ANDAs, and certain BLAs.	03/15/2021 – TRC warnings begin
12/17/2017 – Studies that start on/after require standardized data for commercial INDs.	09/15/2021 – TRC rejections begin

Submissions that do not pass eCTD validation will be rejected starting Sept. 15th, 2021

Even if your study started prior to the dates for data standards requirements above, it must include a trial summary file (contains the study start date and/or reason code for standardized data not applicable) if files are submitted under sections listed in the Technical Rejection Criteria for Study Data*

**For more information, please reference the Technical Conformance Guide*

FDA TECHNICAL REJECTION CRITERIA FOR STUDY DATA

Error	Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*	High	9/15/2021
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	High	9/15/2021
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections* For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections* For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections*	High	9/15/2021
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports	High	9/15/2021

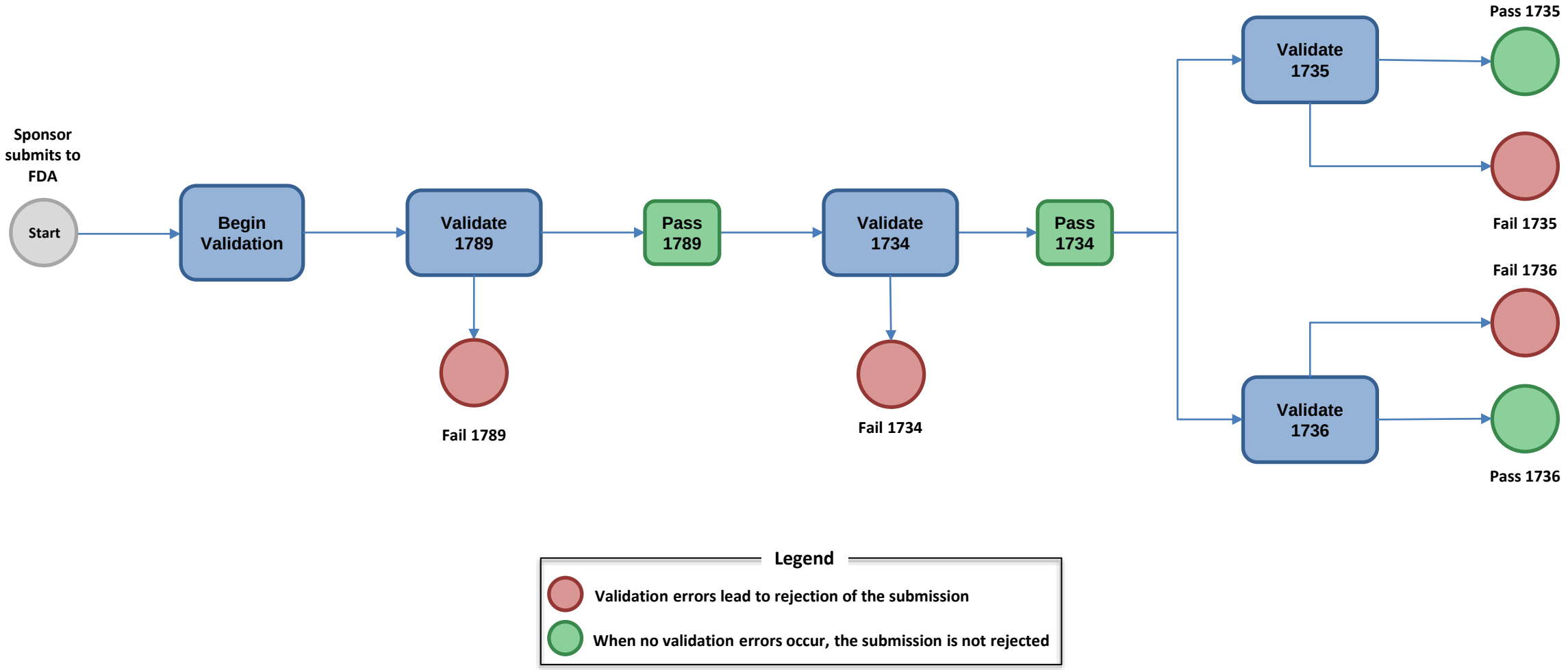
** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

TRC EXPECTATIONS FOR CDER & CBER

Study Start Date	Application Type	Data Type	Modules & Sub-Modules	Expectation by CDER	Expectation by CBER
Prior to or on 17-Dec-16	NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied until March 15, 2023 for non-clinical studies*
Prior to or on 17-Dec-16	NDA, BLA, ANDA	Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
Prior to or on 17-Dec-17	Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied until March 15, 2023 for non-clinical studies*
Prior to or on 17-Dec-17	Comm. INDs	Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will not be applied	
After 17-Dec-16	NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS with standardized data	Rejection criteria will not be applied until March 15, 2023 for non-clinical studies*
After 17-Dec-16	NDA, BLA, ANDA	Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will be applied; submit a full TS with standardized data	
After 17-Dec-17	Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS with standardized data	Rejection criteria will not be applied until March 15, 2023 for non-clinical studies*
After 17-Dec-17	Comm. INDs	Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will not be applied	

** Technical Rejection Criteria for Study Data (Revised 03/15/21) states: "Rejection criteria will not be applied."*

TRC VALIDATION RULE FLOW



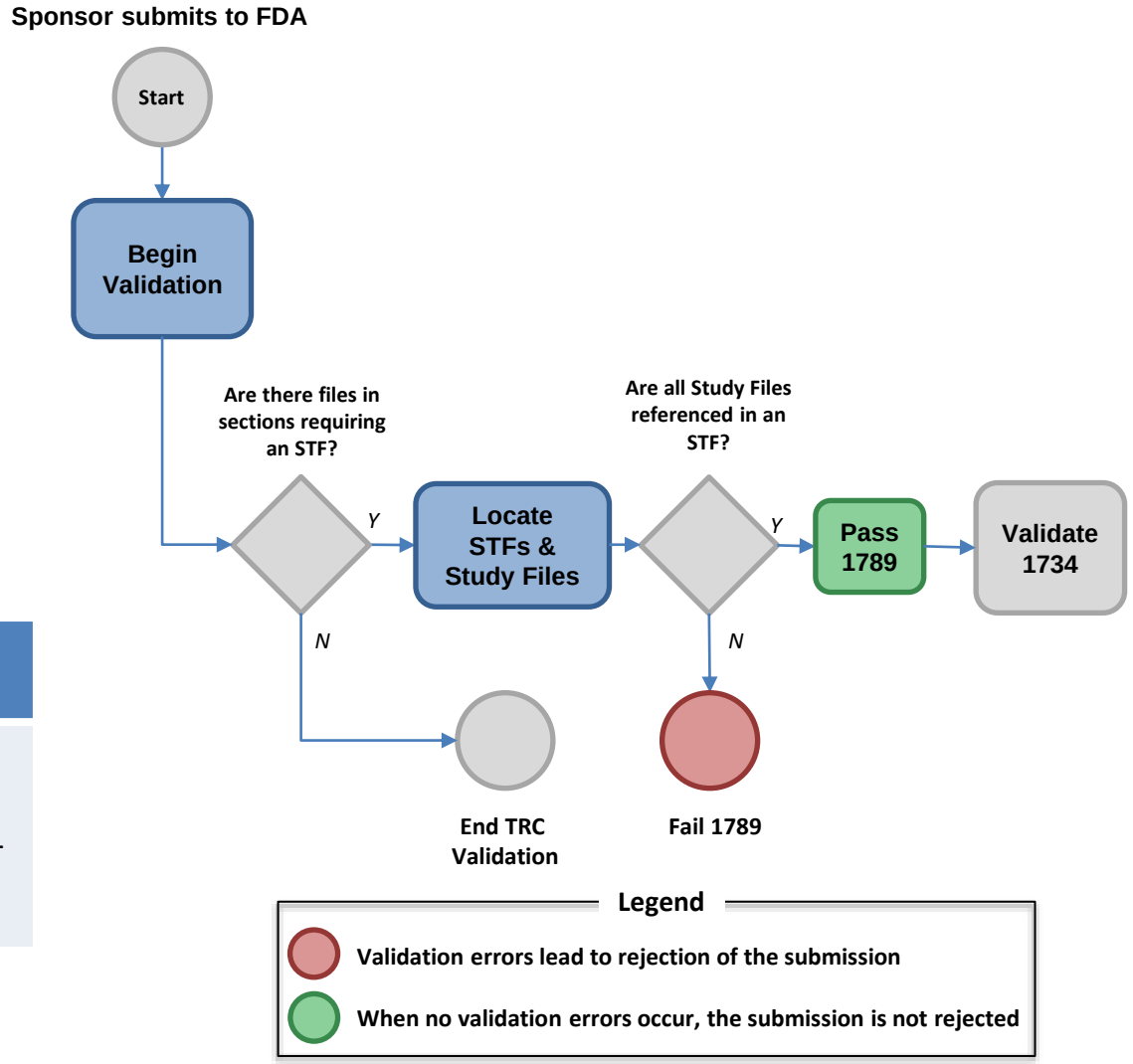
TRC VALIDATION RULE FLOW: RULE 1789

Rule 1789

✓ All study files are included in a Study Tagging File (STF)

- The STF provides information on the study, including the Study Title, Study ID, and the types of files (file tags) included with the study
- The STF links all study files in a submission to a study

Error	Description	Severity Level	Effective Date
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports	High	9/15/2021

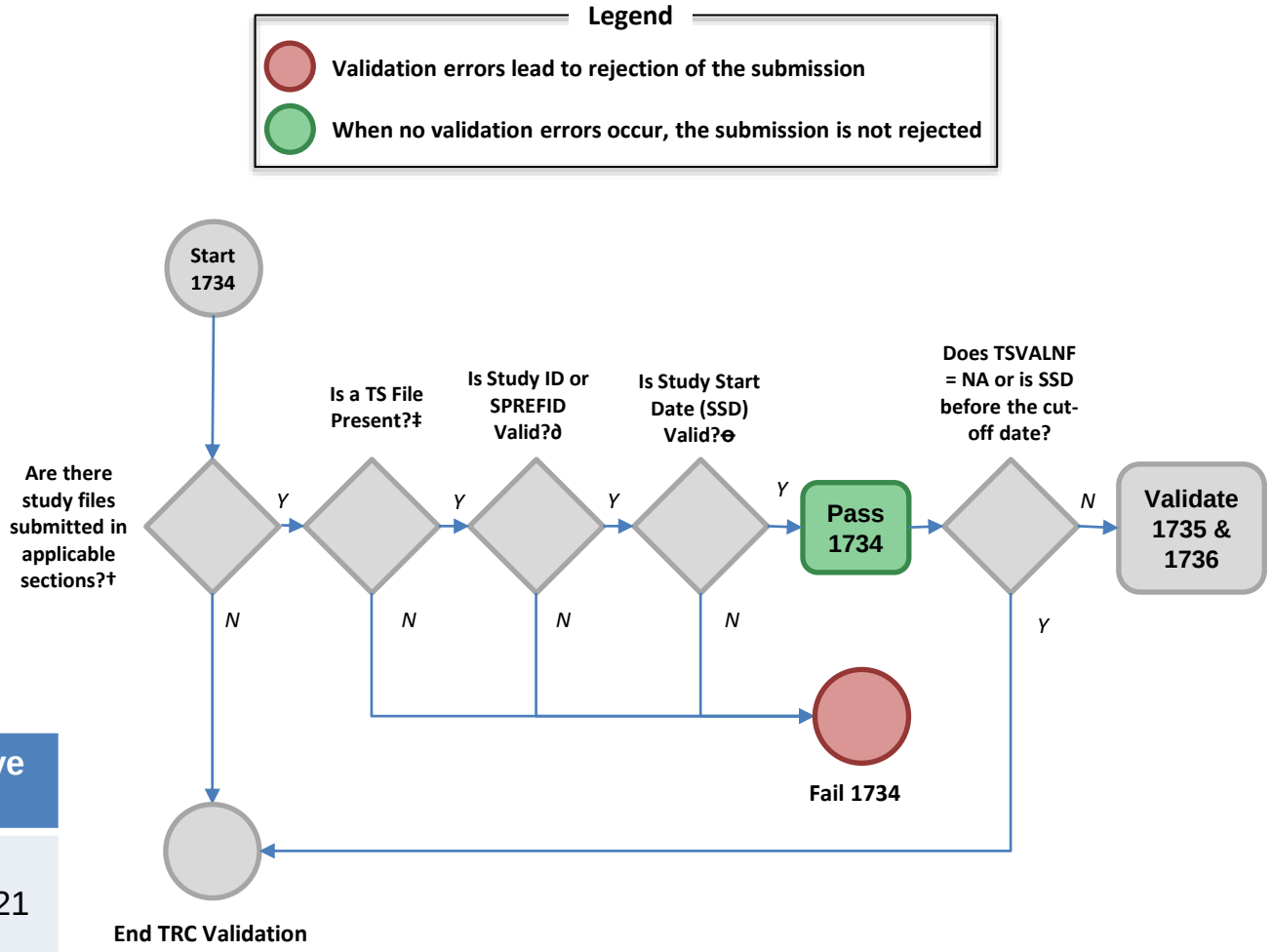


TRC VALIDATION RULE FLOW: RULE 1734

Rule 1734

- ✓ Trial Summary Dataset (ts.xpt) is present
- ✓ Study ID (or SPREFID) matches STF Study ID
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format

- The study start date is key to determining whether standardized datasets are required and if TRC should be applied
- A Simplified ts.xpt is a simple way to provide the study start date when a full ts.xpt is not being submitted



Error	Description	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*	High	9/15/2021

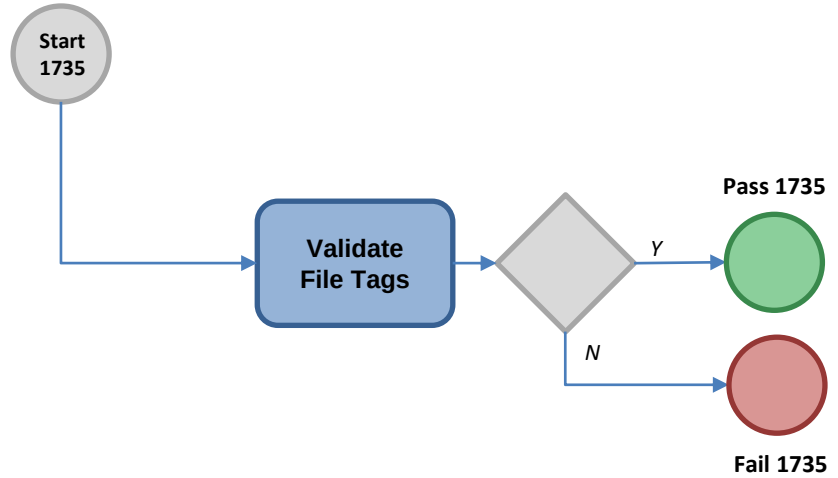
** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4 | Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2*
† XPT file type submitted in M5 or any file type submitted in M4 that has a file tag of "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"
‡ TS file does not need to be in the current sequence if it has been previously submitted and referenced by the STF
∂ Study ID or SPREFID should match the STF Study ID
⊖ Valid Study Start Date in ISO 8601 format (i.e. YYYY-MM-DD)

TRC VALIDATION RULE FLOW: RULE 1735

Rule 1735

- ✓ Standardized dataset domains (e.g. adsl.xpt, dm.xpt) are tagged as:
  - "data-tabulation-dataset-sdtm" for SDTM
  - "analysis-dataset-adam" for ADaM
  - "data-tabulation-dataset-send" for SEND
- ✓ Define.xml files are tagged as:
  - "data-tabulation-data-definition" for SDTM & SEND
  - "analysis-data-definition" for ADaM

- File tags specify file types for all study files
- File tags enable identifying files essential to the regulatory review process



Error	Description	Severity Level	Effective Date
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	High	9/15/2021

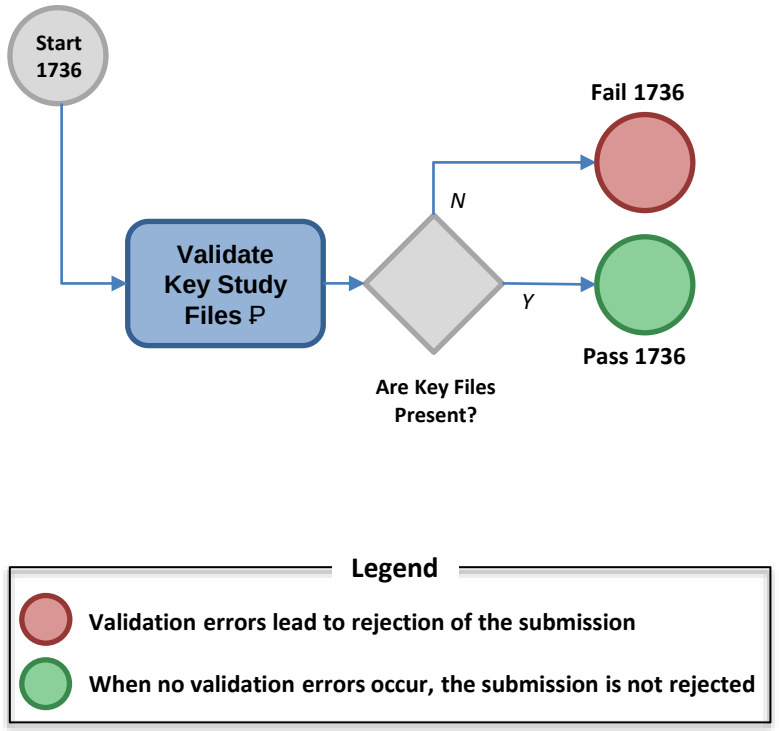
** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4 | Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2*

TRC VALIDATION RULE FLOW: RULE 1736

Rule 1736

- ✓ Define.xml and dm.xpt are present for SEND and SDTM studies
- ✓ Define.xml and adsl.xpt are present for ADaM studies

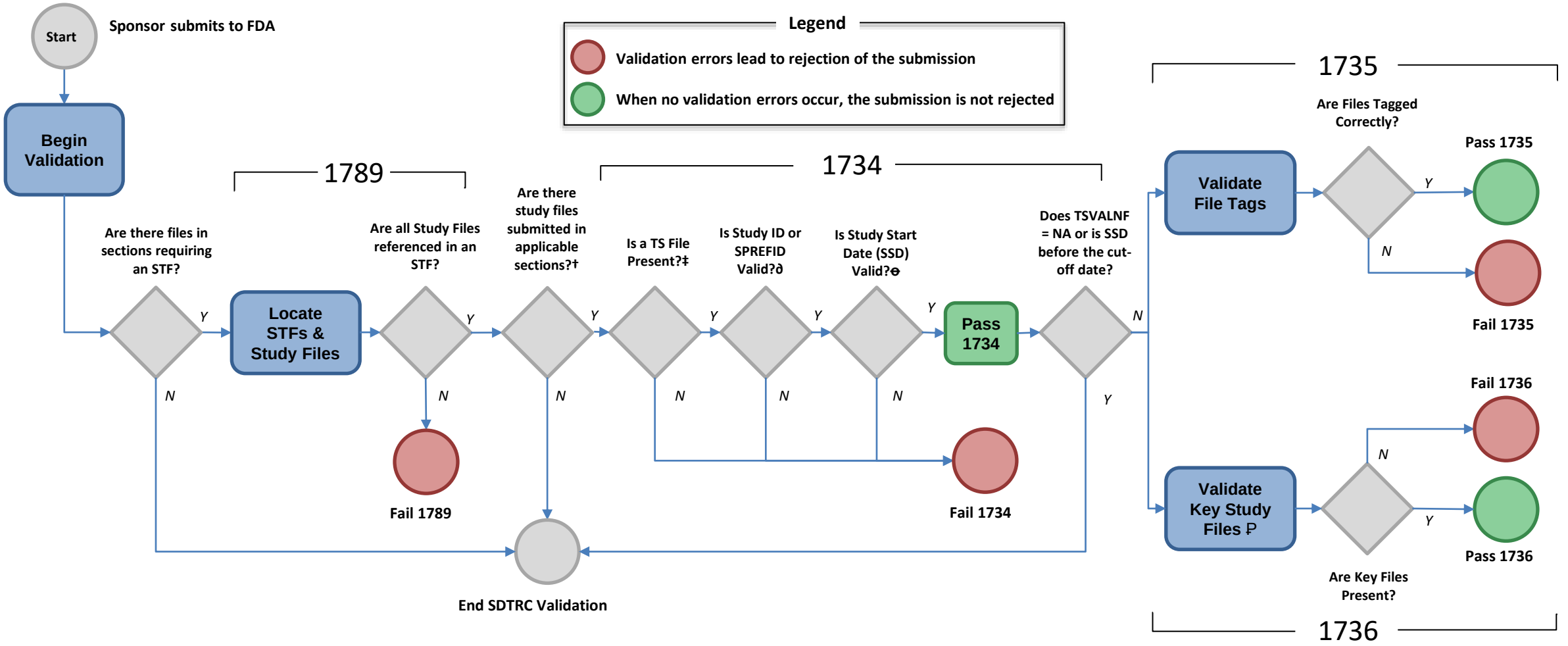
- The DM domain and ADSL domain datasets are required in order to identify subjects and groups within a study or studies
- Define.xml file contains metadata associated with study data domains



Error	Description	Severity Level	Effective Date
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections* For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections* For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections*	High	9/15/2021

** Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4 | Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2*
Ꝑ Key Files are dm.xpt or adsl.xpt and corresponding define.xml

TRC VALIDATION RULE FLOW



† XPT file type submitted in M5 or any file type submitted in M4 that has a file tag of "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"
‡ TS file does not need to be in the current sequence if it has been previously submitted and referenced by the STF
∂ Study ID or SPREFID should match the STF Study ID
⊖ Valid Study Start Date in ISO 8601 format (i.e. YYYY-MM-DD)
₱ Key Files are dm.xpt or adsl.xpt and corresponding define.xml

TRC WARNING METRICS

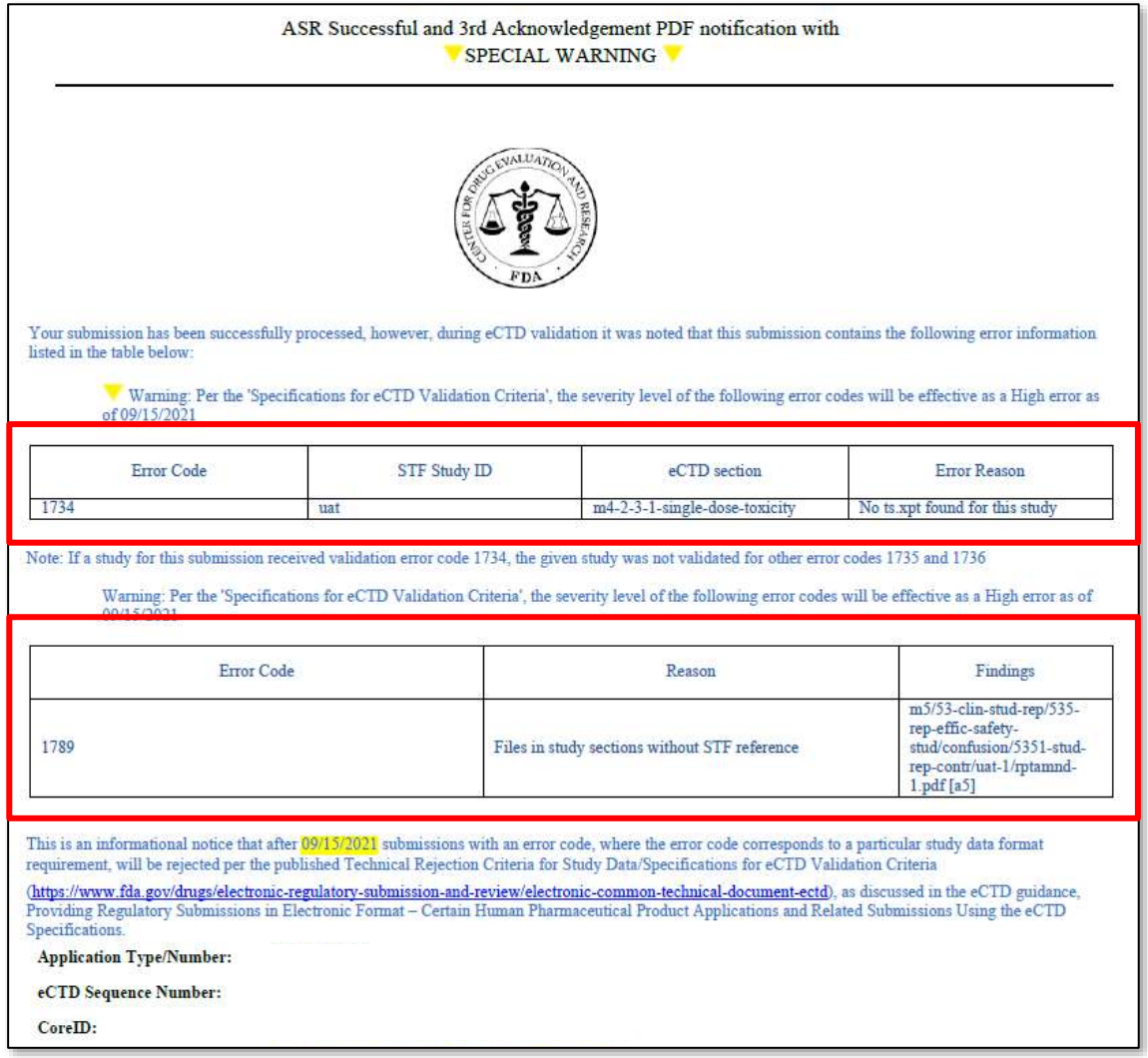
As of March 15, 2021 CDER and CBER have started sending warning notices to applicants who made submissions which failed eCTD validations cited in the TRC.

CDER'S WARNING MESSAGES TO SPONSORS

Sponsors who submit to CDER will receive warnings in the ESG 3rd Acknowledgement from FDA when a TRC error is identified in submissions received between March 15th and Sept. 15th, 2021.

Warnings will specify each error and provide:

- Error Code
- Error Reason
- STF Study ID
- eCTD Section (if applicable)



ASR Successful and 3rd Acknowledgement PDF notification with
SPECIAL WARNING

Your submission has been successfully processed, however, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

Error Code	STF Study ID	eCTD section	Error Reason
1734	uat	m4-2-3-1-single-dose-toxicity	No ts.xpt found for this study

Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes 1735 and 1736

Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 09/15/2021

Error Code	Reason	Findings
1789	Files in study sections without STF reference	m5/53-clin-stud-rep/535-rep-effic-safety-stud/confusion/5351-stud-rep-contr/uat-1/rptamnd-1.pdf [a5]

This is an informational notice that after 09/15/2021 submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Application Type/Number:

eCTD Sequence Number:

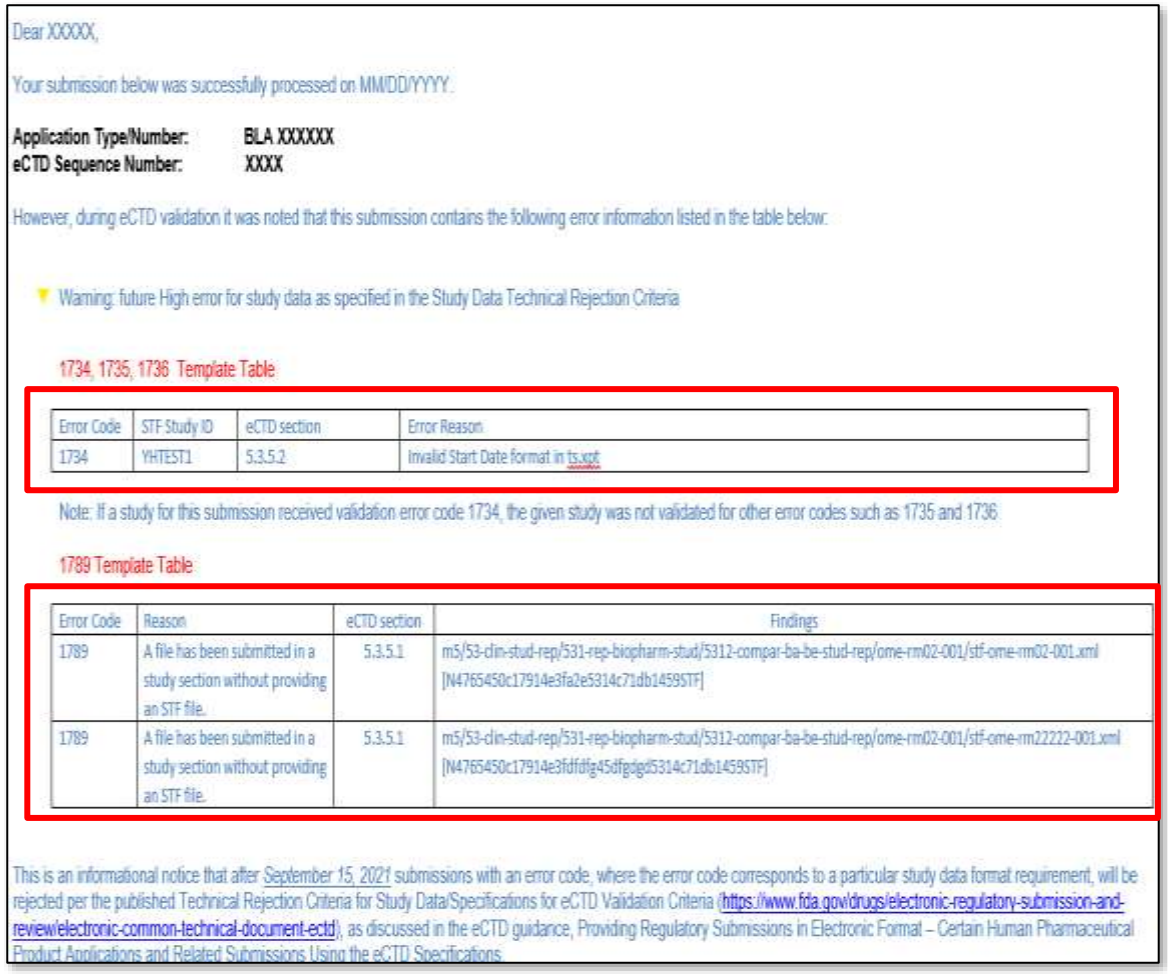
CoreID:

CBER'S WARNING MESSAGES TO SPONSORS

Sponsors who submit to CBER will receive warnings from the CBER-edata account.

Warnings will specify each error and provide:

- Error Code
- Error Reason
- STF Study ID (if applicable)
- eCTD Section



Dear XXXXX,

Your submission below was successfully processed on MM/DD/YYYY.

Application Type/Number: BLA XXXXXX
eCTD Sequence Number: XXXX

However, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

Warning: future High error for study data as specified in the Study Data Technical Rejection Criteria

1734, 1735, 1736 Template Table

Error Code	STF Study ID	eCTD section	Error Reason
1734	YHTEST1	5.3.5.2	Invalid Start Date format in ts.xpt

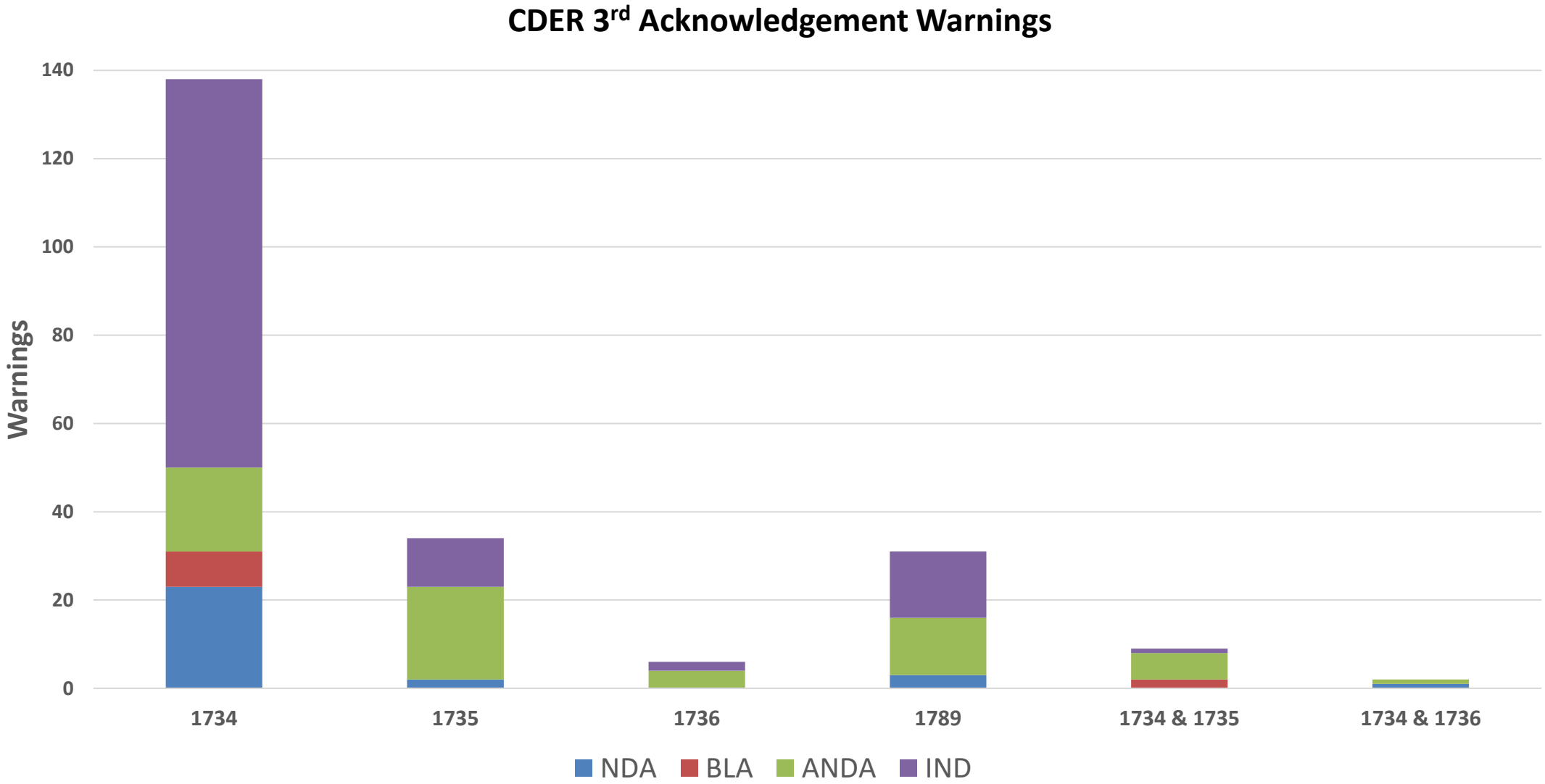
Note: If a study for this submission received validation error code 1734, the given study was not validated for other error codes such as 1735 and 1736

1789 Template Table

Error Code	Reason	eCTD section	Findings
1789	A file has been submitted in a study section without providing an STF file.	5.3.5.1	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm02-001.xml [N4765450c17914e3fa2e5314c71db1459STF]
1789	A file has been submitted in a study section without providing an STF file.	5.3.5.1	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/ome-rm02-001/stf-ome-rm22222-001.xml [N4765450c17914e3fdfdfg45dfgdgd5314c71db1459STF]

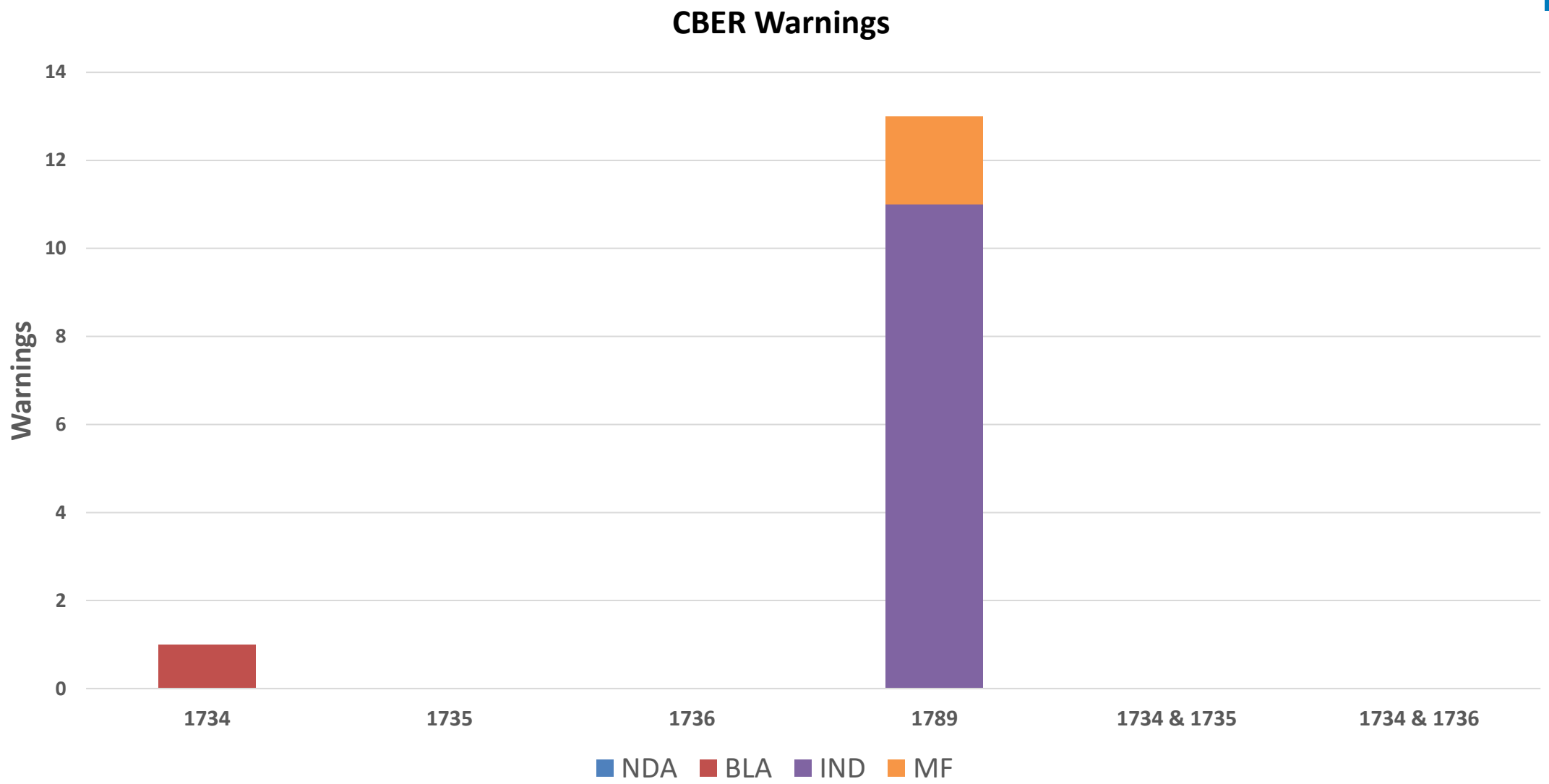
This is an informational notice that after September 15, 2021 submissions with an error code, where the error code corresponds to a particular study data format requirement, will be rejected per the published Technical Rejection Criteria for Study Data/Specifications for eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

WARNINGS FROM CDER



Notes: *Metrics generated from data between March 15, 2021 and April 17, 2021*
Error 1789 applies to all application types

WARNING EMAILS FROM CBER



Notes: *Metrics generated from data between March 15, 2021 and April 17, 2021*
CBER SEND mandatory requirement starts March 15, 2023
Error 1789 applies to all application types

AGENDA

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- Overview of the Technical Rejection Criteria (TRC) & Effective Date
- TRC Warning Metrics
- **CDER SEND Requirements and TRC**
- **Preparing a Study Using the Self-Check Worksheet**
- **Creating a Simplified TS.XPT File**
- **Frequently Asked Questions**

CDER SEND REQUIREMENTS AND TRC

ELECTRONIC STUDY DATA REQUIREMENTS

- For CDER, the following nonclinical study types are required to have SEND datasets as defined by study initiation date:

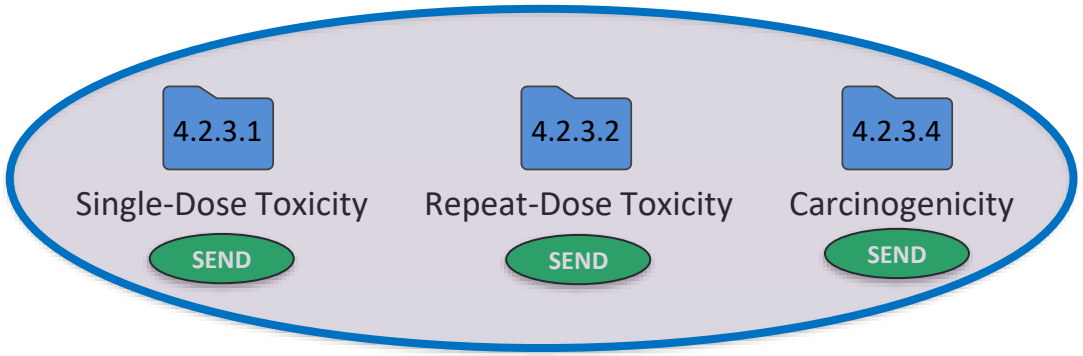
SEND Requirement Dates for Nonclinical Studies Modeled in SEND (Studies started after these dates require SEND datasets)		
Study Types Modeled in SEND	**NDAs/BLAs**	**Commercial INDs**
Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies	December 17, 2016 (SENDIG v3.0) March 15, 2019 (SENDIG v3.1)	December 17, 2017 (SENDIG v3.0) March 15, 2020 (SENDIG v3.1)
Cardiovascular and Respiratory Safety Pharmacology Studies	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)

CDER SEND REQUIREMENTS, ECTD STRUCTURE, AND THE TRC

Module 4
Nonclinical Study Reports

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3 Toxicology
- 4.3 Literature References

SEND is currently required for single-dose toxicity, repeat-dose toxicity, carcinogenicity, CV and RE safety pharmacology studies

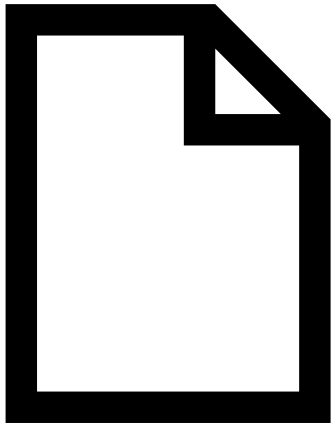


For nonclinical studies, the current Technical Rejection Criteria (TRC) will only apply to eCTD Modules 4.2.3.1 (single-dose toxicity), 4.2.3.2 (repeat-dose toxicity), and 4.2.3.4 (carcinogenicity).

SEND OR SIMPLIFIED TS.XPT (TRIAL SUMMARY)

TRC Applied

- 4.2.3.1 Single-Dose Toxicity
- 4.2.3.2 Repeat-Dose Toxicity
- 4.2.3.4 Carcinogenicity



Nonclinical Study Report

Automated Process

SEND (Full ts.xpt)

SEND Requirement based on Study Type (supported SENDIG) and Study Initiation Date (see FDA Data Standards Catalog)

-OR-

Simplified ts.xpt

Needed when SEND is not required:

1. Study Initiation Date is prior to requirement date
2. A Study Initiation Date is Not Applicable (see Section 8.2.2 of the Study Data Technical Conformance Guide)

Neither SEND (TS) nor simplified ts.xpt = TRC Rejection

PREPARING A STUDY USING THE SELF-CHECK WORKSHEET

TOOLS FOR INDUSTRY

FDA has developed tools to help sponsors meet updated study data standard requirements and provide more transparency on the validation process.

1. Study Data Self-Check Worksheet

- Helps sponsors understand criteria for submissions with study data to pass TRC validations
- Dynamically guides sponsors to prepare study data files according to TRC requirements

2. Simplified TS File Creation Guide & Simplified TS File Generator Utility (PHUSE)

- Helps sponsors easily generate a Simplified TS file to provide a Study Start Date for a study

3. Technical Rejection Criteria for Study Data (Revised March 2021)

- Clarifies the requirements for eCTD Validation of submissions with study data
- Provides a validation table and examples in Appendix 1 and Appendix 2 to illustrate the requirements

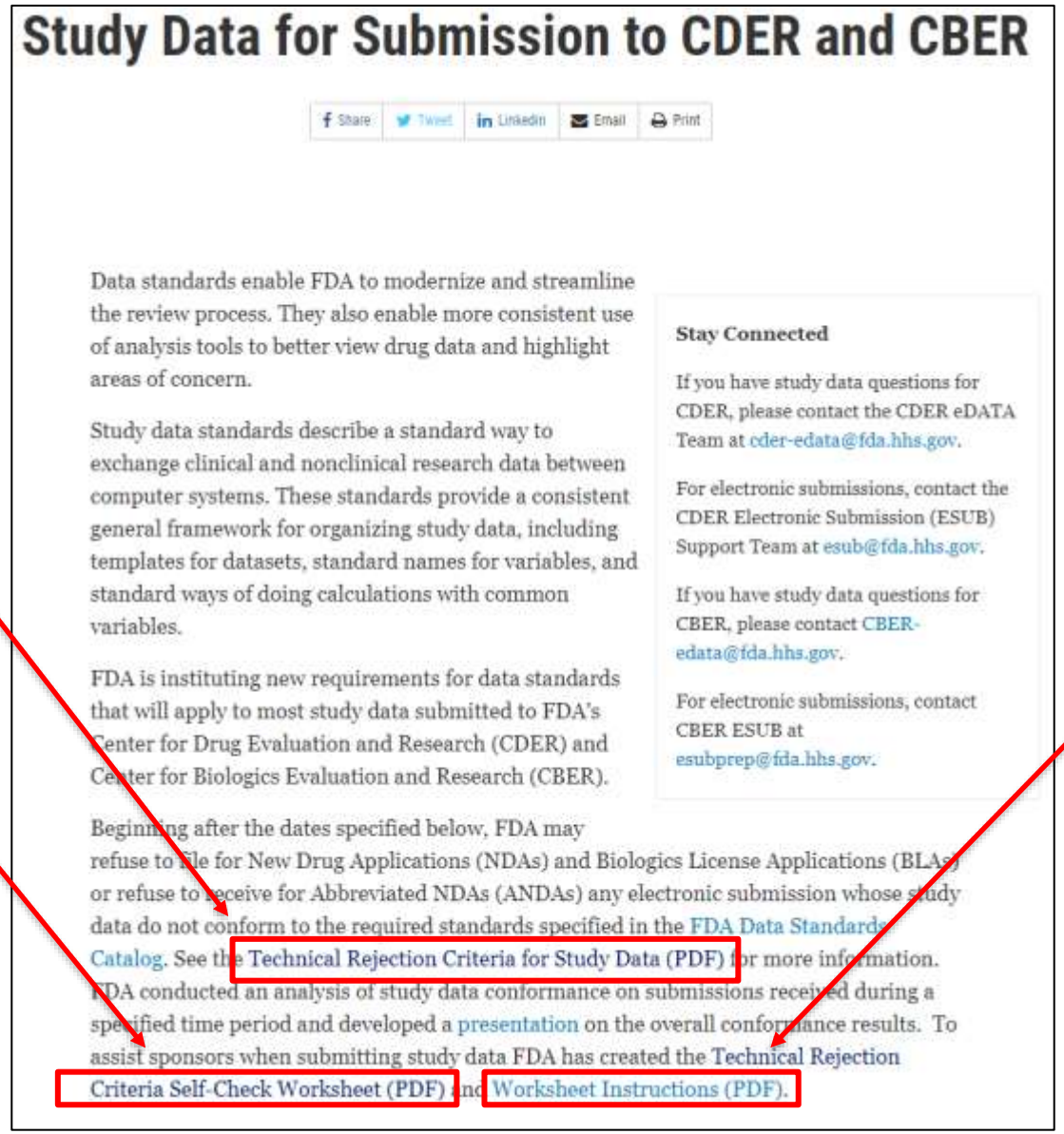
STUDY DATA FOR SUBMISSION TO CDER & CBER

[Study Data for Submission to CDER and CBER Web Page]

[Technical Rejection Criteria for Study Data]

[Technical Rejection Criteria Self-Check Worksheet]

[Technical Rejection Criteria Self-Check Worksheet Instructions]



Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the Technical Rejection Criteria for Study Data (PDF) for more information. FDA conducted an analysis of study data conformance on submissions received during a specified time period and developed a presentation on the overall conformance results. To assist sponsors when submitting study data FDA has created the Technical Rejection Criteria Self-Check Worksheet (PDF) and Worksheet Instructions (PDF).

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

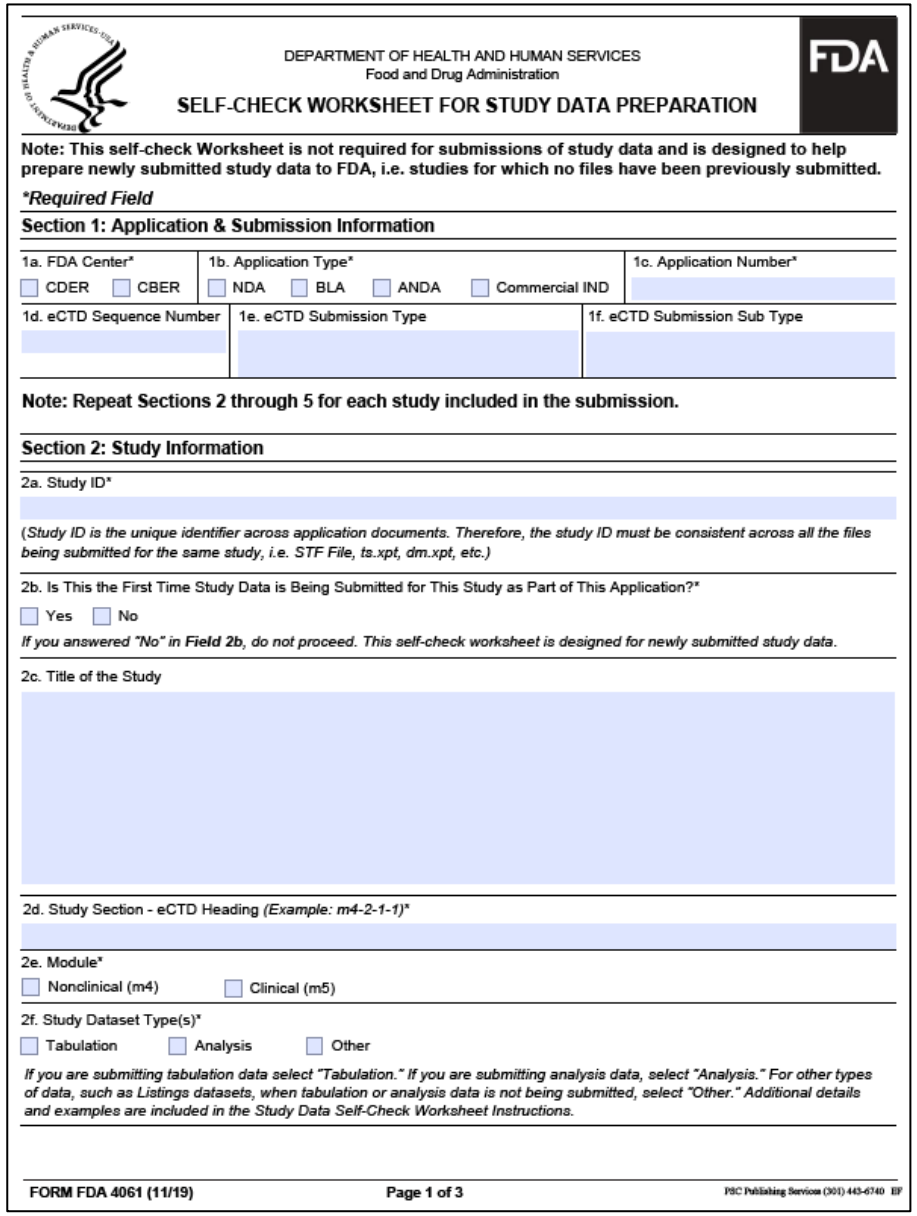
For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

OVERVIEW OF THE SELF-CHECK WORKSHEET

- Designed to walk sponsors through each step of TRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Helps sponsors prepare study data to submit to the FDA for the first time

Technical Rejection Criteria Self-Check Worksheet

Self-Check Worksheet Instructions



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION

Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.

**Required Field*

Section 1: Application & Submission Information

1a. FDA Center*	1b. Application Type*	1c. Application Number*
☐ CDER ☐ CBER	☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	

1d. eCTD Sequence Number	1e. eCTD Submission Type	1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*

☐ Yes ☐ No

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

2c. Title of the Study

2d. Study Section - eCTD Heading *(Example: m4-2-1-1)**

2e. Module*

☐ Nonclinical (m4) ☐ Clinical (m5)

2f. Study Dataset Type(s)*

☐ Tabulation ☐ Analysis ☐ Other

If you are submitting tabulation data select "Tabulation." If you are submitting analysis data, select "Analysis." For other types of data, such as Listings datasets, when tabulation or analysis data is not being submitted, select "Other." Additional details and examples are included in the Study Data Self-Check Worksheet Instructions.

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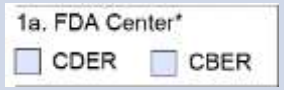
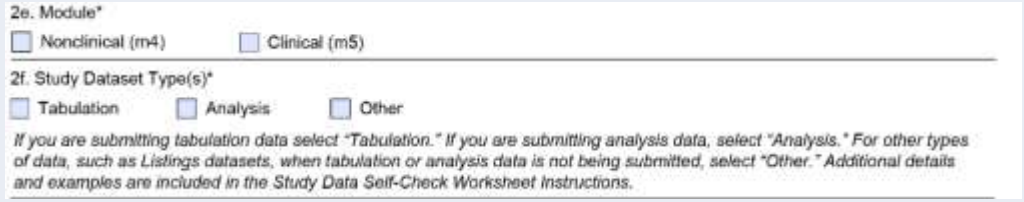
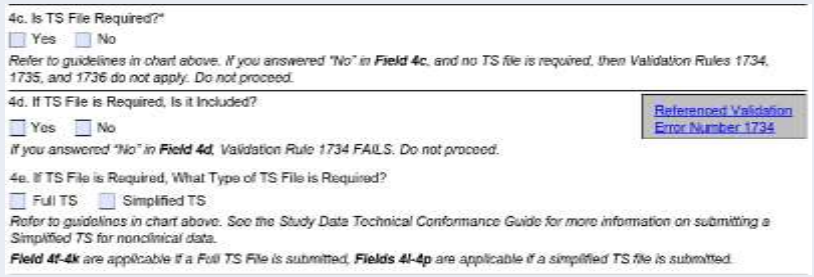
SECTIONS OF THE STUDY DATA SELF-CHECK WORKSHEET

Section	Contents	Example(s)
1	**Application & Submission Information** • Provides high level information about the application and submission	
2	**Study Information** • Provides more detailed information about the specific study	
3	**STF File Information** (1789 Validation Error) • Provide information about STF file	
4	**TS File Information** (1734 Validation Error) • Provide information about ts.xpt file with study start date	
5	**Standardized Dataset Information** (1735 & 1736 Validation Error) • Provide information about SEND or STDM and/or ADaM dataset and define.xml • Provide information about STF File-tags	 Study Start Date / Application Type / Standardized Datasets Required? Prior to or on 17-Dec-16 / NDA, BLA, or ANDA / Not Required After 17-Dec-16 / NDA, BLA, or ANDA / Required Prior to or on 17-Dec-17 / Commercial IND / Not Required After 17-Dec-17 / Commercial IND / Required

Note: Sections 2 through 5 are repeated for each study.

REAL WORLD SCENARIOS DEMONSTRATED IN THE TRC SELF-CHECK WORKSHEET

1. A Commercial IND non-clinical study which began prior to December 17, 2017 is submitted to FDA and the study files are referenced in a Study Tagging File (STF), a ts.xpt dataset is not included in the study. The Study Data Start Date cannot be determined, and the study fails validation 1734.

2. An NDA clinical study in standardized format is submitted to FDA and the study files are referenced in a Study Tagging File (STF). The ADaM dataset in Module 5 contains a define.xml file and an adsl.xpt file and they are appropriately tagged in the STF. The study passes validation 1736.

Demo videos can be found on: Study Data for Submission to CDER and CBER

CREATING A SIMPLIFIED TS.XPT FILE

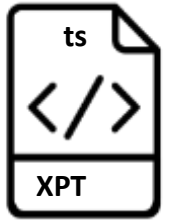
HOW TO CREATE A SIMPLIFIED TS.XPT FILE

- Sponsors should submit a simplified ts.xpt even if datasets are not submitted for a non-clinical study
- Sponsors should submit a ts.xpt file (either simplified or full ts.xpt) for clinical studies that contain .xpt file(s)
- To understand if a simplified ts.xpt file is required, please review the TRC Self-Check Worksheet
- FDA has created a step-by-step Simplified ts.xpt Creation Guide on how to create a simplified ts.xpt using free and open-source tools such as R or Python.

SIMPLIFIED TS.XPT FILES

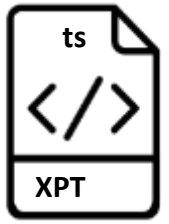
Example of a Simplified TS file submitted for a non-clinical study with study-id "S107" in the STF file:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC	2014-10-26	



Example of a Simplified TS file submitted for a non-clinical study with study-id "S107" in the STF file without a study start date:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC		NA



SIMPLIFIED TS.XPT FILE CREATION GUIDE

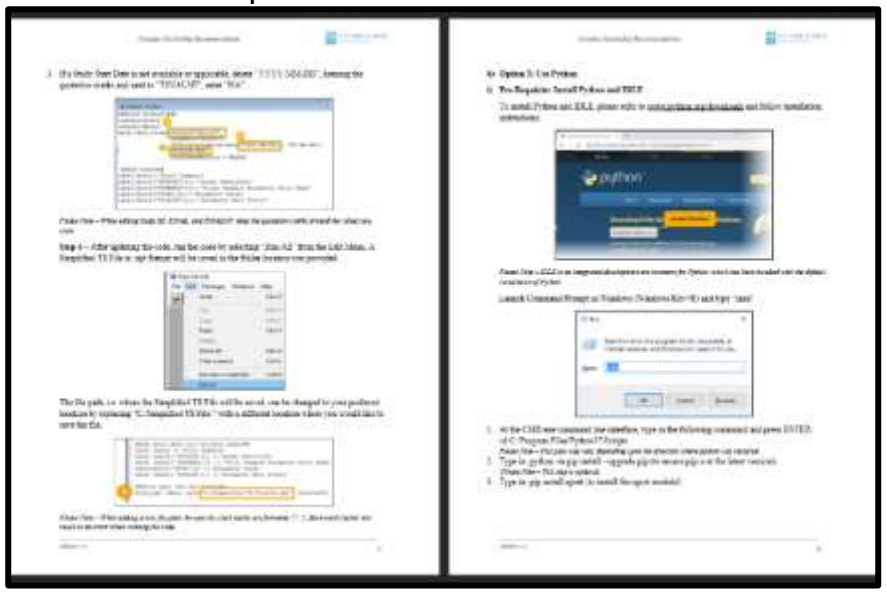
- The Simplified ts.xpt Creation Guide is a resource that FDA provided industry to help create a simplified TS file using free and open-source software such as*:
  - R
  - Python
- This guide provides step by step instructions to install the necessary software to create and view the simplified ts.xpt file
- Users can simply copy paste the code from the guide to generate the simplified ts.xpt
- This guide is intended for users with non programming background to create the simplified ts.xpt with ease
- The guide is available on the FDA's web page, *Study Data for Submission to CDER and CBER*
- Additionally, a publicly available tool was developed by PHUSE to generate simplified ts.xpt files:

  Simplified ts.xpt File Generator (*https://geotiger.shinyapps.io/07_genTS/*)

Study Data TCG references the Guide:

> Information on the Technical Rejection Criteria and the FDA Data Standards Catalog may be found at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
>
> The CDER resource 'Creating Simplified ts.xpt Files', using free and open-source software may be found at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
>
> If there are any questions as to the appropriate use of the simplified ts.xpt file, contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

Simplified TS File Creation Guide:



**The listed software is not an exhaustive list*

CREATING A SIMPLIFIED TS.XPT FILE DEMONSTRATION IN R

Creating a Simplified ts.xpt file using R:

- Study ID: XYZ123
- Study Type: Non-clinical
- Study Start Date: 2011-01-01

Demo video can be found on: Study Data for Submission to CDER and CBER

FREQUENTLY ASKED QUESTIONS

FREQUENTLY ASKED QUESTIONS

Q: We received a 3rd Acknowledgement for a submission with TRC errors. Can you please confirm the submission was not rejected and was received by the review division?

A: Your submission was successfully processed and assigned for review. The additional information in the acknowledgment is a warning to inform you that submissions with TRC errors do not pass validation and will be rejected effective 09/15/21.

FREQUENTLY ASKED QUESTIONS

1734

Q: We received a warning with the validation code of 1734 . Please provide some insight as to why we received an error?

A: The error, validation code 1734, indicates that your submission did not include a ts.xpt with information on the study start date for the study in Module 4. Please include a simplified ts.xpt with the study start date with a non-clinical study when study reports are submitted.

FREQUENTLY ASKED QUESTIONS

1734

Q: We submitted a study with a TS file. Please provide some insight as to why we received an error?

A: The TS file for your study was not named ts.xpt and therefore generated a 1734 error. Please be aware that only “ts.xpt” is an acceptable file name for a trial summary dataset.

or

A: The 1734 error for the study submitted was caused by an incorrectly formatted study start date. The study start date in ts.xpt files should be formatted, “yyyy-mm-dd.”

FREQUENTLY ASKED QUESTIONS

1735

Q: We received 1735 errors for the study we submitted. The dm.xpt, adsl.xpt, and other .xpt dataset files were tagged “analysis-data-definition” and “data-tabulation-data-definition.” Can you please explain why we received these errors?

A: You received the 1735 errors because .xpt datasets and associated define.xml files require different file tags. Define files should be tagged as either “analysis-data-definition” or “data-tabulation-data-definition.” But .xpt datasets should be tagged “analysis-dataset-adam” or “data-tabulation-dataset-sdtm.”

FREQUENTLY ASKED QUESTIONS

1736

Q: We submitted DM and ADSL files in the initial filing for our study. If we submit the required information to these studies in future submissions, would we need to resubmit those datasets, or will the validation check past sequences?

A: The validation checks past sequences so there is no need to resubmit those datasets if they have been previously submitted for the study, unless you need to make updates to the files.

FREQUENTLY ASKED QUESTIONS

1789

Q: We received a 1789 error for our submission. How can we fix this in the future?

A: Validation rule 1789 checks that all files submitted in a study section are included in a Study Tagging File (STF). In future submissions, ensure that all study files have an associated STF file.

REFERENCES

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [Oct 2020]
  - Study Data Technical Conformance Guide [March 2021]
  - FDA Data Standards Catalog [March 2021]
  - Link: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
- **Study Data for Submission to CDER and CBER**
  - Technical Rejection Criteria For Study Data [March 2021]
  - Technical Rejection Criteria Self-Check Worksheet
  - Technical Rejection Criteria Self-Check Worksheet Instructions
  - Link: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
- **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry**
  - Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

IN SUMMARY…

- TRC will be implemented on September 15, 2021
- FDA warning sponsors since March 15 if submission fails TRC (CDER provides notice in ESG 3rd Ack)
- If documents are submitted under TRC application sections in modules 4 or 5, then a trial summary file may be required to pass validation, regardless of study type or start date. See TRC for details to avoid rejection!
- FDA has developed tools to help sponsors pass TRC

QUESTIONS

For questions please contact:

Study Data Questions:
edata@fda.hhs.gov

eCTD Questions:
esub@fda.hhs.gov

ANSWERS TO YOUR QUESTIONS

We will now respond to as many of your questions as our time allows.

If you have not already submitted your question, please type it into the Q&A Pod in the lower right corner